BWG

BIPHENYL WORK GROUP

1850 M Street, N.W., Suite 700
Washington, D.C. 20036
(202) 721-4162 - (202) 296-8120fax

March 9, 2005

Dr. Oscar Hernandez
Director, Risk Assessment Division
Environmental Protection Agency
7403M
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460

Dear Dr. Hernandez:

Re: SOCMA Biphenyl Work Group's response to EPA comments on the HPV Challenge Submission: BIPHENYL

The SOCMA Biphenyl Work Group (BWG) thanks the Environmental Protection Agency for reviewing and commenting on the draft test plan and dossier for Biphenyl (CAS# 92-52-4). With respect to EPA's recommendation that an in vitro chromosomal aberration study be conducted, we believe the available data from the Sofuni et al. paper should suffice. We also believe the additional algae data provided should suffice. Since we have been unable to obtain all of the information requested, we will wait to submit the dossier and test plan until that information is obtained. The BWG has specific comments to issues raised by EPA below.

SUMMARY OF EPA COMMENTS

1. Health Effects. Adequate data are available for the acute, repeated-dose, reproductive and developmental toxicity, and gene mutation endpoints for the purposes of the HPV Challenge Program. The submitted data for chromosomal aberrations are inadequate for the purposes of the HPV Challenge Program. Unless the submitter can provide robust summaries for additional studies to support a weight- of-evidence approach, an *in vitro* test following OECD TG 473 is needed to address this endpoint. The submitter also needs to address deficiencies in the robust summaries.

Response: The BWG has obtained more information on the in vitro chromosomal aberration tests and has added that information to the dossier. We are also attempting to obtain more information on the in vivo chromosomal aberration study. As soon as we obtain that information it will be added to the dossier.

2. Ecological Effects. The submitted toxicity data for the fish and invertebrate endpoints are adequate for the purposes of the HPV Challenge Program. Data for the algal endpoint are inadequate.

Response: An algae study of a mixture of 26% biphenyl with the remainder of diphenyl oxide was found. Robust summaries of this mixture and pure diphenyl oxide have been added to the dossier. The results of these two studies are nearly identical and support our view that there is essentially no difference in the toxicity of biphenyl and diphenyl oxide.

Test Plan

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for the acute, repeated-dose, reproductive and developmental toxicity, and gene mutation endpoints. The submitter needs to provide missing details in the robust summaries.

Response: Where possible we have added additional information. Many studies conducted prior to incorporation of GLPs or published reports do not provide the level of detail EPA has requested. In these cases we have added a statement to clarify that no additional information is available.

Genetic toxicity (chromosomal aberrations). EPA does not consider this endpoint to be adequately addressed by the submitted cytogenetic assay using Chinese hamster DON cells because of the following deficiencies cited by the submitter: (1) the absence of testing with a metabolic activation system, (2) uncertainty about whether the highest concentration was cytotoxic, (3) the lack of test concentrations above 1mM (OECD TG 473 recommends a high concentration of 10mM), and (4) the examination of an insufficient number (100) of metaphases (half the recommended number).

The submitter identified but did not provide robust summaries for several other chromosomal aberration studies, including one (Sofuni et al., 1985) in which positive results were observed with metabolic activation. EPA recommends that the submitter provide robust summaries for these studies if they can support a weight-of-evidence approach. If not, EPA recommends an *in vitro* test following DECO TG 473 to address this endpoint.

Response: We have obtained the Sofuni et al., 1985 study and have prepared a robust summary in the dossier. We are also attempting to obtain more detail on the in vivo chromosomal aberration study. We believe the negative response in the in vivo chromosomal aberration study negates the need to conduct another in vitro chromosomal aberration study.

Ecological Effects (fish, invertebrates, and algae)

Fish. In order to enhance the key fish study, the submitter needs to provide adequate robust summaries for other acute fish toxicity tests mentioned in the test plan (see p. 9).

Response: Robust summaries of the acute fish toxicity studies have been added to the dossier.

Algae. Data for this endpoint are inadequate. The 3-hour study duration of both submitted studies fell short of the 72-hour or 96-hour duration recommended by DECO 201. Testing is needed using measured concentrations.

Response: An algae study of a mixture of 26% biphenyl with the remainder of diphenyl oxide was found. Robust summaries of this mixture and pure diphenyl oxide have been added to the dossier. The results of these two studies are nearly identical and lend credence to the argument that there is essentially no difference in the toxicity of biphenyl and diphenyl oxide.

Specific Comments on the Robust Summaries

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

For those studies summarized from information in the CICAD documents, revised robust summaries need to be based on the primary reference study reports.

Response: Where possible we have updated the dossier with information based on primary reference reports. In some cases, we have not been able to obtain primary reference reports. In the case of the two year mouse chronic toxicity/carcinogenicity study, the paper is expected to be published soon. We have requested the author provide us a copy of the paper when it is published. If we obtain a copy prior to resubmitting the dossier, we will prepare a robust summary.

Acute toxicity. The robust summary for the acute oral toxicity study in male and female Sprague-Dawley rats (Monsanto Project No. Y -76-263, 1976) is missing details, including test substance purity, age of the animals, method of dose administration, control group data, and statistical analysis and standard deviation.

Response: We have provided everything we can extract from the report. We have made the note in the Methods section 'No additional information provided.'

Repeated-dose toxicity. The robust summary for the 750-day study (Ambrose et al., 1960) is missing details, including test substance purity, statistical methods and statistical significance of results. There is also an error in recording the highest dose tested in the robust summary.

Response: Detailed examination of the published paper does not provide additional details. We have made the note in the Methods section 'No additional information provided.' We have corrected the highest dose level tested in the robust summary.

The robust summaries for the two 104-week bioassays in rats and mice (JBRC, 1996) are missing details, including the test guideline or standardized test method used, test substance purity, complete lists of organs and tissues weighed and histologically examined, statistical methods and statistical results.

Response: The rat study has been published and additional details were provided in the published report. This information has been added to the dossier. As previously mentioned, the mouse chronic toxicity/oncogenicity study is expected to be published shortly. The author has confirmed that it was conducted via OECD guideline 453.

Genetic toxicity. The robust summary for the bacterial reverse mutation assay is missing details, including test substance purity and GLP compliance.

Response: NTP did not provide this information on their website. We have made the note in the Methods section 'No additional information provided.'

Reproductive toxicity. The robust summary for the three-generation study in Long-Evans male and female rats is missing details, including test substance purity, the test guidelines or standard methods used, GLP compliance, sex of the pups, number of live births and stillbirths, details on infertile animals, estrus cycle and sperm parameter data, complete list of male and female reproductive organs and tissues harvested, preserved and examined histopathologically, and statistical methods used.

Response: The authors did not provide this level of detail in their report. We have made the note in the Methods section 'No additional information provided.'

The robust summary for the oral study in male and female rats of unspecified species (Ambrose et al., 1960) is missing details, including test substance purity, test guideline or standardized method used, GLP compliance, sex of pups, body weight data, number of live births and stillbirths, details on infertile animals, and statistical analyses of reproductive data. Test concentrations were also inconsistently reported in the summary.

Response: The authors did not provide this level of detail in their report. We have made the note in the Methods section 'No additional information provided.'

In the robust summaries for the 2-year studies in male and female Fischer 344/DuCrj rats and Cjr: BDF 1 mice, the submitter speculates about the male and female reproductive organs that might have been examined. There is no explicit substantiation that any of the reproductive organs were weighed, or that a full range of reproductive organs (e.g., ovaries, testes, epididymides, and accessory sex organs) was examined histologically. In addition, the test concentrations reported in the robust summaries are not consistent with the concentrations reported in the cited secondary reference (CICAD No.6, Biphenyl). Additional information missing from one or both of the robust summaries includes test substance purity, test guideline or standard method used, GLP compliance, control groups and responses, complete list of organs examined and weighed, and the details of the statistical methods and analyses performed.

Response: We have been able to ascertain the rat bioassay by the Japan Bioassay Research Center was conducted according to OECD 453 guideline. The carcinogenicity guideline, adopted in 1981, calls for the examination of gonads, uterus, accessory gonads and female mammary gland. In addition, the gonads of 10 rats/sex/dose level were weighed. We will update the dossier.

Developmental toxicity. The robust summary for the oral study in female Wistar rats is missing details on test substance purity and the test guideline or standardized method used. The robust summary for the oral study in female CLFP (ICI strain) outbred mice is missing details, including the test substance purity, data for developmental endpoints examined (e.g., number of corpora lutea, number and type of implantations, fetal body weight, and sex ratio), and the results of statistical analyses for some parameters.

Response: The purity of the test material for the oral study has been added to the dossier. The oral study was conducted prior to OECD guidelines but followed the intent of the guidelines adopted in 1981.

For the mouse study, the purity for technical grade material was 99.8%. The additional requested material was extracted from the report whenever possible. However, some information, such as number of corpora lutea was not reported. The number of implantations for each litter was used as a surrogate.

Ecological Effects (fish. invertebrates. and algae)

The input parameters used for ECOSAR to derive toxicity values reported in the test plan for fish, invertebrates, and algae need to be reported in the robust summaries.

Response: This information has been entered in each section.

Fish. Missing study details include test guideline followed, purity of the test substance, and loading rate of the fish. Although two controls (vehicle and water only) were reportedly used, results were provided for only one control. It is unclear which control values are being reported.

Response: The study was conducted according to a Test Rule 40 CFR Part 799 Federal Register Vol 50#177 Thursday 12 Sept. 1985. The purity of the test material was >99.1%. Information was provided to allow loading rates to be calculated. Since the acetone control and water control survival data were identical, only one value was presented. We agree this wasn't clear and have added a footnote stating the data is applicable to both control groups.

Invertebrates. The test guideline followed and loading rate of the daphnids were not reported in the robust summary of the key study.

Response: The study was conducted according to a Test Rule 40 CFR Part 799 Federal Register Vol 50#177 Thursday 12 Sept. 1985. The loading rate information has been provided.

The Biphenyl Work Group (BWG) believes the comments raised by the agency have been satisfactorily addressed. Again we thank you for the opportunity to update our HPV submission.

Sincerely;

John F. (Jack) Murray, CAE
Executive Director

cc: W. Penberthy
M. E. Weber